TRANSMITTAL OF APPEAL BRIEF	Docket No. TMT-10902/04

In re Application of: Michael T. Trese

Application No.	Filing Date	Examiner	Group Art Unit
10/068,314-Conf. #8834	February 6, 2002	M. F. Desanto	3763

Invention: METHOD FOR VITREOUS LIQUEFACTION

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed: September 6, 2007 .

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/Avery N. Goldstein, Ph.D./ Dated: September 6, 2007

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Attorney Docket No. TMT-10902/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF APPEALS AND INTERFERENCES

Applicant:	Michael T. Trese et al.	
Serial No.:	10/068,314	Group Art Unit: 3763
Filed:	February 6, 2002	Examiner: Matthew F. DeSanto
For:	METHOD FOR VITREOUS LIQUEFACTION	

APPELLANTS' APPEAL BRIEF UNDER 37 CFR §41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I. Real Party in Interest

The real party in interest in this appeal is the assignee, NuVue Technologies, Inc.

II. Related Appeals and Interferences

Appellant is aware of no appeals or interferences pending or otherwise related to the present appeal.

III. Status of the Claims

The present application was filed with 24 claims. Claims 25-28 were added by amendment. Claims 11-12 and 22-23 have been canceled. Claims 1-10, 13-21, and 24-28 are pending, rejected, and under appeal. Claims 1 and 14 are the independent claims.

IV. Status of Amendments Filed Subsequent Final Rejection

No after-final amendments have been filed.

V. Summary of the Claimed Subject Matter

Independent claim 1 relates to a process for vitreous liquefaction (page 3, lines 1-2) comprising delivery of plasmin into the vitreous body of an eye (page 3, line 23 – page 4, line 1) and incubating the plasmin in the vitreous for a predetermined amount of time to cause liquefaction (page 4, line 2). Dependent claim 2 is directed to delivery to plasmin by injection (page 6, lines 21-23). Dependent claim 3 is directed to delivery to plasmin by induction (page 6, lines 21-23). Dependent claim 4 is directed to delivery to plasmin by intraocular device (page 7, lines 1-3). Dependent claim 5 recites the plasmin as human plasmin (page 5, lines 19-20). Dependent claim 6 recites the plasmin as autologous human plasmin (page 5, lines 20-21). Dependent claim 7 recites a Markush group of accompaniments (page 6, lines 17-19). Dependent clam 8 recites the additional step of plasmin inhibitor delivery (page 7, line 4). Dependent claim 9 recites the subject eye having a pathological condition (page 3, line 9). Dependent claim 10 recites a Markush group of eye pathologies (page3, lines 9-12). Dependent claim 13 recites the predetermined amount of time for incubation being between 10 minutes and 2 hours (page 5, line 14). Dependent claim 25 recites suctioning the liquefied vitreous from the eye (page 8, line 15). Dependent claim 26 recites the suction performance through a 25 or finer gauge instrument. (page 4, line 2).

Independent claim 14 recites delivery of an autologous plasmin into the vitreous of an eye (page 6, line 5) and incubating the autologous plasmin in the vitreous body for a predetermined amount of time to cause liquefaction (page 5, line 14 – page 6, line 2). Dependent claim 15 is directed to delivery to plasmin by injection (page 6, lines 21-23). Dependent claim 16 is directed to delivery to plasmin by induction (page 6, lines 21-23). Dependent claim 17 is directed to delivery to plasmin by intraocular device (page 7, lines 1-3). Dependent claim 18 recites a Markush group of accompaniments (page 6, lines 17-19). Dependent clam 19 recites the additional step of plasmin inhibitor delivery (page 7, line 4). Dependent claim 20 recites the subject eye having a pathological condition (page 3, line 9). Dependent claim 21 recites a Markush group of eye pathologies (page3, lines 9-12). Dependent claim 24 recites the predetermined amount of time for incubation being between 10 minutues and 2 hours (page 5, line 14). Dependent claim 27 recites suctioning the liquefied vitreous from the eye (page 8, line 15). Dependent claim 28 recites the suction performance through a 25 or finer gauge instrument.

(page 4, line 2).

VI. Grounds of Objection/Rejection to Be Reviewed on Appeal

A. The rejection of claims 1-7, 9, 10, 13-18, 20, 21 and 24 under 35 U.S.C. §103(a) over Trese et al. (Ophthalmology, Vol. 105, Issue 9, 1 September 1998, pp. 1617-1620), hereinafter referred to as Trese et al. (Ophthalmology).

B. The rejection of claims 8, 19, and 25-28 under 35 U.S.C. §103(a) over Trese et al. (Ophthalmology) as detailed above further in view of Trese et al. (American Academy of Ophthalmology, ISSN 1607-1610), hereinafter referred to as Trese et al. (American).

C. The rejection of claims 8 and 19 under 35 U.S.C. §103(a) over Trese et al. (Ophthalmology) as detailed above further in view of Trese et al. (American Academy of Ophthalmology, ISSN 1607-1610), hereinafter referred to as Trese et al. (American).

VII. Argument

The Examiner's Position

The Examiner has based the rejection of claims 1-7, 9, 10, 13-18, 20, 21, and 24 under 35 U.S.C. §103(a) as obvious over Trese et al. (Ophthalmology). Trese et al. (Ophthalmology) is cited for teaching the delivery of autologous human plasmin into a vitreous body of an eye and then incubating the eye. Trese et al. (Ophthalmology) is further cited for teaching the use of a dose of 0.4 IU of plasmin. The Examiner in an Office communication dated March 24, 2005 states:

> At the time of the invention it would have been obvious for one of ordinary skill in the art to modify the teachings of Trese et al. because it is well known in the medical field art to vary the dose size that would be injected into a patient, since medication usually depends on the size of the patient as well as the area in which the injection will occur. This concept is well known in the research art and can be seen in the previous cited prior art.

The Examiner has based the rejection of claims 8, 19, and 25-28 under 35 U.S.C. §103(a) as being unpatentable over Trese et al. (Ophthalmology) as applied to the claims above, and further in view of Trese et al. (American). The Examiner believes motivation to combine the

references is found in the skill of one of ordinary skill in the art:

> Trese et al. (Ophthalmology) discloses the claimed invention but fails to specifically point out the use of a plasmin inhibitor and the actual size of the needle being used to remove the liquefaction that occurred in the eye.
>
> Trese et al. (American) discloses the use of a plasmin for the liquefaction of the eye as well as the use of small gauge needles for sucking material out of the eye and the use of a plasmin inhibitor to reduce to the activity of the plasmin that was injected into the eye.
>
> At the time of the invention it would have been obvious for one of ordinary skill in the art to combine the teachings of Trese et al. (Ophthalmology) with Trese et al. (American) because Trese et al. (American) provides further explanation as to why those steps are necessary. Trese et al. (American) also discloses the level of skill in the medical art since it is well known in the art to perform these steps.

Appellant's Position

A. Rejection of Claims 1-7, 9, 10, 13-18, 20, 21 and 24.

The Examiner improperly uses hindsight reconstruction to extend the limited teaching of Trese et al. (Ophthalmology) beyond treatment of pediatric macular holes by separation of the vitreous from the retina to liquefaction of the vitreous for which the prior art provides no reasonable expectation of success. When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention;

(D) Reasonable expectation of success is the standard with which obviousness is determined; and

(E) The Declarations made of record have not been accorded proper weight.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The claimed invention as a whole:

Considering the instant claimed invention as a whole, independent claims 1 and 14 state that less than 0.4 units to 0.1 units of plasmin is used in a human eye, and incubated to create a liquefied vitreous. Thus, the administration of plasmin is claimed to liquefy the vitreous independent of whether the dose results in detachment of congealed vitreous adhered to a retina. Each of these elements is present in the instant claims, and each must be taught or suggested by the prior art to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

However, Trese et al. (Ophthalmology) is wholly limited to teaching a process for macular hole treatment in pediatric patients. A macular hole is a small break in the macula located in the center of the eye's light sensitive material. Macular holes are most commonly treated by pars plana victrectomy, followed by membrane stripping, and administering a tamponade such as a gas bubble or injection of silicon to maintain a seal and promote healing. Essential to this procedure is a separation of the vitreous form the retina and optic nerve head. The administration of high dose plasmin in Trese et al. (Ophthalmology) is solely directed to the belief that "this might allow a less-traumatic separation of the vitreous from the retina and the optic nerve head." (Trese et al. (Ophthalmology), pg. 1617, first column.)

Trese et al (Ophthalmology) teaches that "plasmin enzyme facilitated surgical cleavage of the vitreoretinal interface." (*Id.* at 1618, second column.) Nowhere does Trese et al. (Ophthalmology) teach or suggest liquefaction, or even density reduction of the vitreous. Thus, Trese et al (Ophthalmology) does not teach or suggest all elements of the instant claims and a prima *facie case* of obviousness has not been established.

The prior art as a whole does not suggest the desirability of the instant invention:

Under the objective analysis of section 103 outlined in *Graham*, the scope and content of the prior art are to be determined. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). In determining the scope and content of the prior art the references must be considered as a

whole and must suggest the desirability and thus the obviousness of making the combination. *Hodosh* at n. 5. The test is what the scope and content of the prior art as a whole suggests to one of ordinary skill in the pertinent art. In *In re Wesslau*, the Court of Customs and Patent Appeals cautioned that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965).

One having ordinary skill in the art recognizes that Trese et al. (Ophthalmology) teaches that administration of plasmin results in separation of the vitreoretinal interface. Overall, the purpose, teaching, outcome, and future message of Trese et al. (Ophthalmology) as clearly stated in the discussion at pg. 1620 is that:

> [t]he use of plasmin enzyme in our four cases made the creation of a PVD [posterior vitreous detachment] very simple and atraumatic. The ease and completeness of the PVD facilitated with plasmin enzyme might decrease the incidence of visual field defects that have been reported after macular hole surgery. The use of plasmin enzyme may lead to an increased success rate in repairing idiopathic macular holes.
>
> [I]t appeared that autologous plasmin enzyme used as an adjunct to victrectomy facilitated removal of the cortical vitreous from the retinal surface.

Thus, a person of ordinary skill in the art recognizes that the prior art of Trese et al. (Ophthalmology) teaches only that plasmin is beneficial in promoting detachment of the vitreous from the surrounding tissue.

There is so suggestion in Trese et al. (Ophthalmology) to use a lesser amount of plasmin to induce liquefaction of the vitreous. The Examiner bases his rejection on knowledge in the medical field to "vary the dose size that will be injected into a patient, since medication usually depends on the size of the patient as well as the area in which the injection will occur." (Paper No. 20070623, sec. 3, pg. 2.) However, the cited ordinary practitioner in the art, Trese et al. (Ophthalmology), did not adjust the dose of plasmin according to the difference in size of the patient or the area in which the injection occurs as would be expected by the Examiner's assertion. Trese et al. (Ophthalmology) teaches using 0.4 units of plasmin in the eyes of children ages 11 to 14 years. (p. 1617-18, Methods.) Also, the same practitioner as an author in a second

cited reference, Trese et al. (American), teaches using 0.4 units of plasmin in eyes of adults aged 61-82 years. (p. 1608, Methods.) Trese et al. uses 0.4 units of plasmin in both adult and pediatric eyes, yet cites Verstraeten as guiding the dosage. (Ophthalmology, pg. 1618 (Discussion).) Verstraeten teaches using 1 unit of plasmin in rabbit eyes. Verstraeten, TC, et al., *Arch Ophthalmol*, 1993; 111:849-54. It is recognized in the art that rabbit eyes are smaller than either a child's or an adult's eye. As such, Trese et al. (Ophthalmology) and Trese et al. (American) do not "vary the dose size that will be injected into the patient, since medication usually depends on the size of the patient as well as the area in which the injection will occur." (Paper No. 20070623, sec. 3, pg. 2.) Thus, the prior art, and examples of an ordinary practitioner in the art, did not recognize, teach, or suggest adjusting the dose of plasmin enzyme to account for the size of the patient or the area in which the injection will occur.

Furthermore, adjusting the dose downward as in instant claims 1 and 14 was recognized by an ordinary practitioner as counter to the knowledge in the art. For example, Trese et al. (American) teaches that incomplete and unpredictable liquefaction was obtained in human eyes when 0.4 units plasmin was used. "Liquefaction of the vitreous cavity was graded as large in two eyes, medium in two eyes, and small in five eyes." (p. 1609, Results.) The difference from large to small is cited as less than 25% for small and greater than 75% for large grading. (p. 1608, Surgical Technique.) Thus, the range of liquefaction ranged from nearly none at all to nearly complete levels. The ordinary practitioner recognizes that the dose of plasmin and the time of incubation directly correlate with the magnitude of plasmin effect. "The degree of vitreoretinal separation depends on the concentration and length of exposure to plasmin." Gandorfer, A, et al., *Br J Ophthalmol*, 2001; 85:6-10 (Abstract). Thus, the prior art as a whole, and Trese et al. (Ophthalmology) specifically, recognize that obtaining consistent and efficacious results requires increased plasmin levels. (1 unit, human eyes- Gandorfer, A et al., *Eye*, 2002; 16:95-97; 1-2 units, pig eyes- Gandorfer, A, et al., *Br J Ophthalmol*, 2001; 85:7, first column; 1 unit, rabbit eyes, Hikichi, T, et al. *Retina*, 1999; 19:55-58.) Thus, Trese et al. (Ophthalmology), and the knowledge in the art of plasmin injection into the eye provide no motivation for lowering the plasmin levels as in the instant claims.

In considering the references as a whole, where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541

F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

The prior art of Trese et al. (Ophthalmology) does not teach or suggest a using plasmin to liquefy the vitreous at doses below 0.4 units as in instant claims 1 and 14. Trese et al. (Ophthalmology) teaches using 0.4 units of plasmin, not below this level. Thus, there is no overlap between the teaching of Trese et al. (Ophthalmology) and the instant claims.

Moreover, an ordinary practitioner recognizes that plasmin used below 0.4 units and at or above 0.4 units do not have the same properties. Indeed, Trese et al. (American), an example of an ordinary practitioner, recognizes and teaches that "plasmin enzyme in a dose dependent fashion contributes to liquefaction of the vitreous." (p. 1609, Discussion [*citing* Pendergast SD, et al., *Invest Ophthalmol Vis Sci*, 1996; 37:S195] (emphasis added).) The ordinary practitioner recognizes that greater liquefaction is achieved with greater levels of plasmin whereas lower does of plasmin decrease vitreal liquefaction.

Also, the instant specification makes clear that low doses of plasmin show differential activity by affecting matrix metalloprotease activities, whereas higher levels lead to posterior vitreous detachment. (pg. 4, lines 10-14.) The teaching that 0.4 units of plasmin will lead to some level of PVD in pediatric eyes has no bearing on the function of plasmin in liquefaction by altering, for example, matrix metalloprotease activity as each is served by the differential effect of plasmin after injection.

These distinctions make clear that the liquefaction properties of less than 0.4 units of plasmin and 0.4 units or greater are not the same in either animal or human eyes. Therefore, Appellant submits that a *prima facie* case of obviousness has not been established.

Impermissible Hindsight:

Using hindsight reconstruction, the Examiner has concluded that the present invention is obvious over Trese et al. (Ophthalmology). However, an Examiner may not, because of doubt that the invention is patentable, resort to speculation, unfounded assumption or hindsight

reconstruction to supply deficiencies in the factual basis for the rejection. See *In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 177 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). Rather, in determining obviousness, "the [E]xaminer can satisfy the burden of showing obviousness of the combination 'only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" *In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002), citing *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

Appellant submits that the claimed invention is nonobvious over Trese et al. (Ophthalmology) since the separation of the vitreous from the dissimilar retinal tissue is a less effective vitreal treatment, as compared to the claimed invention. The liquefaction of the vitreous represents a dissolution of the gelled vitreous, not necessarily a detachment. As there is neither a teaching nor contemplation that plasmin injected into a subject eye according to Trese et al. (Ophthalmology) is able to induce vitreous liquefaction, it is submitted that this higher level of performance as recited in claim 1 and claim 14 is not obvious in light of Trese et al. (Ophthalmology).

The notion that one skilled in the art would be motivated to deliver a dose of plasmin of less than 0.4 units into a vitreous body of a subject human eye and incubate the plasmin for a predetermined amount of time *to create a liquefied vitreous* is not provided by the prior art of Trese et al. (Ophthalmology). Appellant submits that the only motivation for the above described process is found in the pending application and hindsight reconstruction is improper.

No reasonable expectation of success:

Appellant submits that Trese et al. (Ophthalmology), and the prior art as a whole, provide no reasonable expectation of success using less than 0.4 units of plasmin as a liquefaction agent in the human eye. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Also, the court in *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), held that the there claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling

methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.

In contrast to the facts of *In re O'Farrell*, Trese et al. (Ophthalmology) provides neither a suggestion to modify the prior art to produce the instantly claimed invention nor any evidence that the modification would be successful. Indeed, Trese et al. (Ophthalmology) is absolutely silent regarding using plasmin to liquefy the vitreous and restricts its teaching to posterior vitreous detachment in the treatment of macular holes.

Looking outside the cited prior art to the knowledge of an ordinary practitioner in the art as evidenced by the relevant literature, it becomes clear, contrary to Examiner's assertion, that there is no reasonable expectation of success. In fact, the knowledge of the art is that decreasing plasmin dose is less likely to be successful for vitreous liquefaction. Trese et al. (American) teaches that at the relatively low level of plasmin of 0.4 units, it is entirely unpredictable how much liquefaction will occur, and often little to none is achieved. (p. 1609, Results.) Since the level of plasmin activity "depends on the concentration and length of exposure," an ordinary practitioner in the art recognizes that only by increasing the plasmin levels will there be a reasonable expectation of regular, predictable success. (Gandorfer, A, et al., 2001, Abstract.) This is further evidenced by the statement in Trese et al. (American) that:

> The dose of 0.4 IU of autologous plasmin enzyme, which seems optimal for producing a PVD in humans, does not show the reliable liquefaction of vitreous that was seen in animals. This suggests to us that a vitreous cutter is still necessary to safely remove the partially liquefied vitreous, making space for gas used in the postoperative management of stage 3 macular holes. We believe that this study demonstrates that it is possible to achieve spontaneous posterior vitreous separation and closure of macular holes in the human eye but that liquefaction of the vitreous gel is *variable* in human eyes at the dose of 0.4 IU. (pg. 1610, 1st column, 1st paragraph; emphasis added.)

As the dose of 0.4 units plasmin is variable in producing liquefaction, and an ordinary practitioner in the art recognizes that only by increasing plasmin dose will greater and more reliable liquefaction occur, neither Trese et al. (Ophthalmology) nor the knowledge of the art as evidenced by Trese et al. (American) provide a reasonable expectation of success from administering less than 0.4 units of plasmin in a human eye.

Thus, not only does the cited prior art of Trese et al. (Ophthalmology) not provide any reasonable expectation of success, but the knowledge of an ordinary practitioner in the art at the time the application was filed also reveals that there is no reasonable expectation of success using less than 0.4 units of plasmin as a vitreous liquefaction agent. Without a reasonable expectation of success in either the cited prior art or the knowledge of an ordinary practitioner in the art at the time the application was filed, a *prima facie* case of obviousness is not established.

Proper Weight Has Not Been Accorded to the Declarations of Record:

A declaration of Michael K. Hartzer was made of record on 9 May 2003, was considered insufficient on the basis of "the examiner still believes the product is the same. There is no evidence to show that the product is a streptokinase-plasmin in the reference as opposed to the 'plasmin' that is claimed in this invention" (Paper No.8, pages 3 -4, section 7).

Additional declarations of Michael K. Hartzer and Patrick J. Gaffney were subsequently made of record on 10 November 2003. These Declarations were similarly dismissed on belief that the product claimed is the same. (Paper No. 13, pages 3 -4, section 7).

With the establishment of a prima facie case of obviousness, rebuttal evidence must be considered. In Re John B. Sullivan and Findlay E. Russell, (CAFC, 2006-1507, decided 29 August 2007, page 9): states:

> Evidence rebutting a prima face case of obviousness can include: "evidence of unexpected results," Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1369 (Fed. Cir. 2007), evidence "that the prior art teaches away from the claimed invention in any material respect," In re Peterson, 315 F.3d 1325, 1331 (Fed. Cir. 2003), and evidence of secondary considerations, such as commercial success and long-felt but unresolved needs, WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999). When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence. See In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability"); In re Sernaker, 702 F.2d 989, 996 (Fed. Cir. 1983) ("If, however, a patent applicant presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.").

By failing to consider the submitted declaratory evidence, Applicant contends that error was committed. Specifically, the declarations in question establish the material reported in Trese

et al. (Ophthalmology) as "plasmin" was in fact a complex of streptokinase-plasminogen that has lower enzymatic activity than the subject matter of the pending claims. The information provided in these declarations must be taken at face value as sworn declarations. Appellant submits that the examiner's response to these declarations and the data included therein was improper in failing to articulate how these declarations do not rebut the outstanding rejections. *In Re John B. Sullivan and Findlay E. Russell, (CAFC, 2006-1507, decided 29 August 2007.*

With the statements made of record in these declarations given proper weight, Trese et al. (Ophthalmology) when practiced fails to teach plasmin at all, since the actual active enzyme was the less efficacious steptrokinase-plasminigen complex, and as such the effectiveness of Trese et al. (Ophthalmology) as a reference supporting an obviousness rejection is called into question.

Conclusion:

Trese et al. (Ophthalmology) when taken as a whole provides no motivation or reasonable expectation of success when using less than 0.4 units of plasmin as a vitreal liquefaction agent. The declaratory statements made of record and not given weight successfully refute obviounsness of the pending claims at to this reference. Therefore, Appellant submits that independent claims 1 and 14 are patentable over Trese et al. (Ophthalmology). If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Therefore, Appellant further submits that claims 2-7, 9, 10, 13, 15-18, 20, 21, and 24 are similarly nonobvious.

B. The rejection of claims 8, 19, and 25-28 under 35 U.S.C. §103(a)

Appellant submits that claims 8, 19, and 25-28 are allowable on the basis of dependency from an allowable base claim and incorporates by reference the above remarks with regard to the rejections over Trese et al. (Ophthalmology). Appellant further submits that the prior art reference combination fails to yield the claimed invention of claims 8, 19, and 25-28 not only for the reasons cited above but also based on the fact that a person having ordinary skill in the art has no motivation to combine the teaching of Trese et al. (Ophthalmology) with Trese et al. (American), and Trese et al. (American) teaches away from the claimed invention.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). It is improper to combine references where the references teach away from their combination. *In re Grasselli,* 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Trese et al. (American) teaches that plasmin is inefficient, incapable, and unreliable in producing liquefaction of the vitreous in human eyes at the low dose of 0.4 units. In *In re Wesslau* the Court of Customs and Patent Appeals cautioned that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." 353 F.2d at 241, 147 USPQ at 393. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley,* 27 F.3d 551, 553 (Fed. Cir. 1994); *See also KSR Int'l, Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1739-40 (2007) (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). "[A] reference teaches away from a combination when using it in that combination would produce an inoperative result." *In re Icon Health & Fitness, Inc.*, 2007 U.S. App. LEXIS 18244, 16 (Fed. Cir. 2007).

Appellant asserts that an ordinary practitioner in the art having the combination of references before him is discouraged from using plasmin as an agent to produce liquefaction of the human eye at a dose below 0.4 IU. Trese et al (American) teaches that:

> The liquefaction features of plasmin enzyme are very prominent in animal eyes in a dose-dependent fashion with 0.1 units of plasmin being optimum. The dose of 0.4 IU of autologous plasmin enzyme, which seems optimal for producing a PVD in humans, does not show the reliable liquefaction of vitreous that was seen in animals. This suggests to us that a vitreous cutter is still necessary to safely remove the partially liquefied vitreous, making space for gas used in the postoperative management of stage 3 macular holes. We believe that this study demonstrates that it is possible to achieve spontaneous posterior vitreous separation and closure of macular holes in the human eye but that liquefaction of the vitreous gel is *variable* in human eyes at the dose of 0.4 IU. (pg. 1610, 1st column, first paragraph.) (emphasis added; internal references omitted).

The above statements alone and in combination with the remainder of the reference suggest to an

ordinary practitioner in the art that liquefaction is not reliably achieved using 0.4 IU of plasmin. That using plasmin below 0.4 units produces the inoperable result of reducing both the reliability and extent of vitreous liquefaction. The ordinary practitioner further recognizes the opposite from the prior art, that increased liquefaction is achieved by dose dependently increasing the dose of plasmin administered to the human eye.

As the liquefaction features of plasmin enzyme are taught by Trese et al. (American), and by the knowledge in the art as cited therein, to decrease with lower doses, Trese et al. (American) teaches away from using less than 0.4 units of plasmin as a liquefaction agent by criticizing, discrediting, and discouraging its use. (*See e.g. In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).). An ordinary practitioner is led by Trese et al. (American) to a path of increasing plasmin dose, rather than decreasing dose as stated in instant claims 1 and 14. Therefore, as explained by the Court in *In re Gurley*, 27 F.3d at 553, Trese et al. (American) "may be said to teach away" from using plasmin as in the instant claims.

As Trese et al. (American) teaches away from using plasmin as a liquefaction agent in the human vitreous below a dose of 0.4 units, it is improper to combine Trese et al. (American) with Trese et al. (Ophthalmology). Thus, Appellant submits that a *prima facie* case of obviousness is not present.

C. The rejection of claims 8 and 19 under 35 U.S.C. §103(a)

The examiner bases his rejection of claims 8 and 19 on the assertion that Trese et al. (American) provides motivation for use of "a plasmin inhibitor . . . to control the amount and effectiveness of plasmin [and] the use of a plasmin inhibitor to reduce to the activity of the plasmin that was injection (sic) into the eye (surgical techniques.)" (Paper No. 20070623, sec. 4, pg. 3.) However, Trese et al. (American) and Trese et al. (Ophthalmology) provide no teaching or suggestion for the use of a plasmin inhibitor in the human eye. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580. Thus, in the absence of any teaching or suggestion of the use of a plasmin inhibitor, an ordinary practitioner is not motivated by the combination of Trese et al. (Ophthalmology) and Trese et al. (American) to use a plasmin inhibitor as in the instant invention.

Furthermore, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). Trese et al. (American) teaches that:

> liquefaction features of plasmin enzyme are very prominent in animal eyes in a dose dependent fashion . . . The dose of 0.4 IU of autologous plasmin enzyme, which seems optimal for producing a PVD in humans, does not show the reliable liquefaction of vitreous that was seen in animals. (pg. 1610, 1st column, first full paragraph.)

An ordinary practitioner, thus, recognizes that Trese et al. (American) teaches greater liquefaction achieved by increasing the dose of plasmin delivered to the vitreous, and that the use of a plasmin inhibitor would reduce the extent of liquefaction. As 0.4 IU is taught to unreliably induce vitreal liquefaction, Trese et al. (American) does not teach or suggest an expected beneficial result from using a plasmin inhibitor. To the contrary, an ordinary practitioner draws the inference from the entirety of the teaching of Trese et al. (Ophthalmology) and Trese et al. (American) that a plasmin inhibitor when used in combination with less than 0.4 IU of plasmin would less reliably produce liquefaction of the vitreous in a human eye.

Thus, as a plasmin inhibitor is neither taught nor suggested by Trese et al. (Ophthalmology) or Trese et al. (American) either alone or in combination, no basis exists for a *prima facie* case of obviousness of claims 8 and 19. Appellant submits that claims 8 and 19 are, therefore, nonobvious and directed to patentable subject matter on independent grounds.

Conclusion

In summary, the Examiner's references and combination of references that make up the outstanding rejections include a reference that does not make obvious the claims 1-7, 9, 10, 13-18, 20, 21 and 24. The declaratory evidence of record is more than sufficient to rebut a prime facie case of obviousness, even if one was initially established. Furthermore, the reference Trese

et al. (American) teaches away from the present invention and a motivation to deliver a dose of plasmin of less than 0.4 units in a volume of about 0.1 cubic centimeters into a vitreous body of a human eye and incubate the plasmin in the vitreous body for a predetermined amount of time to create liquefied vitreous is absent, except for within the present application.

Accordingly, the obviousness rejection under 35 U.S.C. §103(a) with regard to claims 1-7, 9, 10, 13-18, 20, 21, and 24 should be reversed. Also, the obviousness rejection under 35 U.S.C. §103(a) with regard to claims 8, 19, and 25-28 should likewise be reversed.

Respectfully submitted,

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APPENDIX A

CLAIMS ON APPEAL

1. A process for human vitreous liquefaction comprising the steps of:

delivering a dose of plasmin in a range of less than 0.4 units to 0.1 units and in a volume of about 0.1 cubic centimeters into a vitreous body of a subject human eye; and

incubating the plasmin in the vitreous body for a predetermined amount of time to create a liquefied vitreous.

2. The process of claim 1 wherein the delivering is by injection.

3. The process of claim 1 wherein the delivering is by infusion.

4. The process of claim 1 wherein the delivering is by sustained release intraocular device.

5. The process of claim 1 wherein the plasmin comprises human plasmin.

6. The process of claim 1 wherein the plasmin comprises autologous human plasmin.

7. The process of claim 1 wherein the plasmin comprises an accompaniment selected from the group consisting of: an enzyme, a glycoprotein, a polysaccharide, an antibiotic, a pharmaceutically acceptable diluent, a pharmaceutically acceptable adjuvant and a pharmaceutically acceptable carrier.

8. The process of claim 1 further comprising the step of delivering a plasmin inhibitor.

9. The process of claim 1 wherein the subject eye has a pathological condition.

10. The process of claim 9 wherein the pathological condition is selected from the group consisting of: diabetic retinopathy, macular hole, macular pucker, intraocular infection, foreign intraocular material and retinal detachment.

13. The process of claim 1 wherein the predetermined amount of time is between ten minutes and two hours.

14. A process for human vitreous liquefaction comprising the steps of:

delivering a dose of plasmin in a range of less than 0.4 units to 0.1 units and in a volume of about 0.1 cubic centimeters comprising autologous plasmin into a vitreous body of a subject human eye; and

incubating the plasmin in the vitreous body for a predetermined amount of time to induce vitreous liquefaction.

15. The process of claim 14 wherein the delivering is by injection.

16. The process of claim 14 wherein the delivering is by infusion.

17. The process of claim 14 wherein the delivering is by sustained release intraocular device.

18. The process of claim 14 wherein the plasmin comprises an accompaniment selected from the group consisting of: an enzyme, a glycoprotein, a polysaccharide, an antibiotic, a pharmaceutically acceptable diluent, a pharmaceutically acceptable adjuvant and a pharmaceutically acceptable carrier.

19. The process of claim 14 further comprising the step of delivering a plasmin inhibitor.

20. The process of claim 14 wherein the subject eye has a pathological condition.

21. The process of claim 20 wherein the pathological condition is selected from the group consisting of: diabetic retinopathy, macular hole, macular pucker, intraocular infection, foreign intraocular material and retinal detachment.

24. The process of claim 14 wherein the predetermined amount of time is between ten minutes and two hours.

25. The process of claim 1 further comprising the step of suctioning the liquefied vitreous from the subject human eye.

26. The process of claim 25 wherein suctioning is performed through a 25 or finer gauge instrument.

27. The process of claim 14 further comprising the step of suctioning the liquefied vitreous from the subject human eye.

28. The process of claim 27 wherein suctioning is performed through a 25 or finer gauge instrument.

APPENDIX B

EVIDENCE

Evidence has been entered under §1.132, namely the sworn Declarations of Michael K. Hartzer ascribed to on May 9, 2003 and October 17, 2003; and the sworn Declaration of Patrick J. Gaffney ascribed to on October 30, 2003. Evidence pursuant to § 1.131 was entered by or relied upon by the examiner was also submitted as part of the sworn Declaration of Michael K. Hartzer ascribed to on October 17, 2003.

Attorney Docket No. TMT-10902/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael T. Trese et al.	
Serial No.:	10/068,314	Group Art Unit: 3763
Filed:	February 6, 2002	Examiner: Matthew F. DeSanto
For:	METHOD FOR VITREOUS LIQUEFACTION	

DECLARATION OF MICHAEL K. HARTZER, Ph.D.

I, Michael K. Hartzer, hereby declare as follows:

1. Currently I am Director of the Trumbull Ophthalmic Research Laboratory at William Beaumont Hospital Research Institute, Royal Oak, Michigan. I have held this position since January 1991. In addition, I have been Director of Research and Development at NuVue Technologies Inc. since May 2000. Prior to these positions, I was a professor of various grades at the Eye Research Institute, Oakland University, Rochester, Michigan from September 1985 until July 2000.

2. I hold Ph.D. and B.S. degrees from Iowa State University. I also have completed post-doctoral training as a Fellow in Ophthalmology and Cell Biology at the Bascom Palmer Eye Institute, University of Miami School of Medicine from July 1984 through September 1985. I have authored or co-authored over 25 scientific publications and over 100 published abstracts in this field. I have been carrying out research on ophthalmic disorders for approximately 12 years.

3. I am a co-inventor on the above-identified patent application, U.S. Patent Application Serial No. 10/068,314 ("the Application") and have read the Office Action dated December 20, 2002 ("the Office Action"). I have also reviewed and am familiar with the reference cited in the Office Action, M.T. Trese, G.A. Williams and M.K. Hartzer, "A New

Approach to Stage 3 Macular Holes" *Ophthalmology* 107(8), 2000, pp. 1607-1611, of which I am a co-author.

4. I understand that pending claims 1-24 of the Application have been rejected under 35 U.S.C. §102(b) as being anticipated over the *Ophthalmology* Vol. 107 article which I co-authored with M.T. Trese and G.A. Williams. I state as a co-author of Trese et al. and having subsequently worked on the current invention that at the time that Trese et al., it was unknown to me and my co-inventors that liquefaction of vitreous gel in the human eye at a dose of 0.4 units of plasmin was highly variable and represented our understanding of the liquefaction process at that time.

5. Subsequent to the publication of Trese et al., I have modified the activation procedure for plasminogen. The work done in 1999 and published in Trese et al. used a 1:1 molar ratio of streptokinase to plasminogen. A 1:1 molar ratio of streptokinase to plasminogen produced a final product that was essentially all streptokinase-plasminogen complex. Subsequent to the publication of Trese et al., I participated in experiments that used a 0.1:1 molar ratio of streptokinase to plasminogen that resulted in a final product containing 90% plasminogen and only 10% streptokinase-plasmin complex. I have strong experimental evidence that plasmin has much higher biological activity within the vitreous than does the streptokinase-plasmin complex.

6. I believe the reason for the higher biological activity of plasmin relative to the streptokinase-plasmin complex is that the complex represents a much larger molecule than plasmin. Such proteins have three-dimensional structures, often the sites on the substrate proteins, such as fibrinogen, laminin, and fibronectin, that contain the correct amino acid sequence to be recognized and cleaved by the enzyme are not on the surface of the molecule and instead are located in a pocket or crevice. The size and stearic constraints associated

with the streptokinase-plasmin complex limits the access of this complex the ability of the streptokinase-plasmin complex to access crevices and pockets within the vitreal substrate.

7. As a result of the formation of free plasmin that has a higher biological activity than the streptokinase-plasmin complex, it is possible according to the present invention to consistently perform liquefaction of the vitreous gel at plasmin doses of 0.4 units or less. The invention of claims 1-24 varies from the teaching of Trese et al. in that in Trese et al. streptokinase-plasmin complex was formed and not free plasmin which, as detailed above, has a greater biological activity toward liquefaction of the vitreous gel.

8. Based on the above considerations, I do not believe that Trese et al. teaches vitreous liquefaction in a human eye at a plasmin dose of less than 0.4 units.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Michael K. Hartzer, Ph.D.

Date: 5/9/03

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Attorney Docket No. TMT-10902/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael T. Trese et al.	
Serial No.:	10/068,314	Group Art Unit: 3763
Filed:	February 6, 2002	Examiner: Matthew F. DeSanto
For:	METHOD FOR VITREOUS LIQUEFACTION	

SUPPLEMENTAL DECLARATION OF MICHAEL K. HARTZER, Ph.D.

I, Michael K. Hartzer, hereby declare as follows:

1. I reaffirm my statements made in my previous declaration of May 9, 2003.

2. Plasmin (PL) is a hydrolytic enzyme that can degrade a variety of proteins in blood and in the vessel wall. An earlier name had been fibrinolysin, which reflects the major activity of plasmin (e.g. the lysis of fibrin). Essentially there is little or no free plasmin in blood, while its enzymatically-inactive proenzyme form, plasminogen (plgn), is present at 2 μM in human plasma. While plasminogen in plasma may be measured by both indirect and direct methods, plasmin activity can only be measured by a direct method. This is reviewed elsewhere (Gaffney PJ, et al. (1977) Haemostasis 6: 72-881). Indirect methods to measure plasminogen involve the conversion of inactive plasminogen to the active plasmin using a variety of well-known activators, notably Streptokinase (SK), Urokinase (UK) and Tissue-type plasminogen activator (t-PA). The resultant active plasmin can be measured using synthetic substrates or natural biological substrates. A number of synthetic substrates, which mimic the natural protein substrate, have been developed in order to make the assay simple and practical. Typically, a chromogenic group is attached to a plasmin-specific peptide with an amide bond. The most commonly used synthetic substrate for plasmin is S-2251 (D-Val-

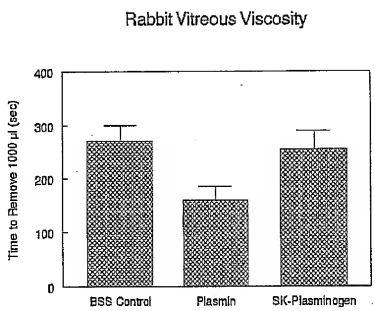
Leu-Lys-p-Nitroanilide Dihydrochloride). When the carboxy-terminal peptide bond is cleaved, the p-Nitroaniline is released from the peptide and is measured as a yellow color at a 405 nm wavelength. The hydrolysis of the S-2251 by plasmin follows a Lineweaver-Burke kinetic relationship. This means that if the substrate (S-2251) is present at a sufficiently high concentration, the amount of color at any one time is dependent upon the amount of enzyme used in the reaction.

3. SK-plasminogen complex levels in plasmin preparation used in Trese et al. (Ophthalmology 2000; 107:1607-11) were prepared as follows: 30 mls of blood were drawn in this study. This yields approximately 15 mls of plasma. Plasminogen levels were quantified in preparations prepared according to the method described in Trese et al. In 10 preparations, an average of 0.75 ± 0.14 nmoles of plasminogen were recovered per ml of plasma. Therefore, in a preparation starting with 15 mls of plasma, the average yield would be 11.3 nmoles of plasminogen. In the method described in Trese et al., 50,000 IU of streptokinase was added to the plasminogen. According to the manufacturer, this represents 10 nmoles of streptokinase. Since streptokinase rapidly forms a 1:1 complex with plasminogen, an average of 88% of the plasminogen would be present as the complex. The other 12% of the plasminogen is converted to plasmin.

4. Subsequent to the publication of Trese et al., I developed strong experimental evidence that plasmin has much higher biological activity than the streptokinase-plasminogen complex. My experimental evidence was confirmed in discussions with Professor Patrick Gaffney, an expert in the field of plasmin fibrinolysis. We believe that the limited proteolytic activity seen in our plasminogen preparations activated with approximately equimolar amounts of streptokinase (Trese et al) was due to the small amount of free plasmin in the preparation. One possible reason for low proteolytic activity of the streptokinase-

plasminogen complex is that it is a much larger molecule than plasmin. Since proteins have three-dimensional structure, it is common that cleavage sites on substrate proteins (e.g. fibrinogen, laminin and fibronectin) are not on the surface of the substrate protein but rather located within an internal crevice, pocket or fold. It is hypothesized that the increased size of the streptokinase-plasminogen complex limits its ability to access such cleavage sites on a substrate protein. As a result of the increase in biological activity for plasmin, the variability in liquefaction of vitreous gel reported in Trese et al. at doses of 0.4 units or less is dramatically reduced when plasmin and not streptokinase-plasminogen complex is the active enzyme.

5. The experimental support for the increased biological activity of plasmin relative to streptokinase-plasminogen complex is shown in the following graph that measures rabbit vitreous viscosity.



BSS, Plasmin (1.0 U) and SK-Plasminogen (1.0 U) were injected into rabbit eyes (n=5). The activity of the injected enzyme preparations was assayed using a synthetic substrate (S-2251). Vitreous liquefaction was assayed 24 hours later by measuring the time required to remove

1000 µl of vitreous with a 25 ga vitrectomy instrument using a standardized procedure for removal. The time required to remove the plasmin vitreous (161 ± 24 sec) was significantly lower than the time required to remove the vitreous in the other groups ($p < 0.05$). This study provides evidence that plasmin liquefies rabbit vitreous whereas SK-plasminogen complex does not.

6. As a result of the steps taken in the present invention to induce the formation of free plasmin that has higher biological activity than the streptokinase-plasminogen complex, it is possible according to the present invention to consistently perform liquefaction of the vitreous gel at plasmin doses of 0.4 units or less. I believe the pending claims vary from the teaching of Trese et al. in that Trese et al. had in actuality as an active enzyme a streptokinase-plasminogen complex and not free plasmin.

7. Based on the above considerations, I do not believe that Trese et al. teaches vitreous liquefaction in a human eye at a plasmin dose of less than 0.4 units.

8. As part of this supplemental declaration, it is intended to establish completion of the invention being claimed in the above-referenced application within the United States at a date prior to December 5, 2001, which is the effective date of X. Lei, X. Shi, and J. Fan, "Posterior vitreous detachment with plasmin in the isolated human eye," Graefe's Arch Clin Exp Opthalmol (2002) 240:56-62 which was cited in the non-final Office Action mailed December 20, 2002.

9. The months leading to our reduction to practice were devoted to experimentation. In support of this statement, appended to this declaration is a page from my laboratory showing some early experimental results indicating that the amount of plasmin, as opposed to a streptokinase-plasminogen complex, varied as a function of preparation technique. This page shows invention prior to the publication of Li et al.

10. The disclosure corresponding to the above-referenced application was forwarded to the law firm of Gifford, Krass, Groh, Sprinkle, Anderson & Citkowski on November 14, 2001. This disclosure resulted in the filing of the above-referenced patent application on February 6, 2002. Appended hereto is a docket page from our attorneys confirming this date.

11. Based on the above considerations, I do not believe that the Li et al. reference published online December 5, 2001 preceded my actual reduction to practice of the invention in this application.

12. This declaration is submitted simultaneous with a request for continued examination and in response to rejections relying on Li et al. in the final Office Action mailed July 30, 2003.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Michael K. Hartzer, Ph.D.

Date: 10/17/03

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Attorney Docket No. TMT-10902/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael T. Trese et al.	
Serial No.:	10/068,314	Group Art Unit: 3763
Filed:	February 6, 2002	Examiner: Matthew F. DeSanto
For:	METHOD FOR VITREOUS LIQUEFACTION	

DECLARATION OF PATRICK J. GAFFNEY

I, Patrick J. Gaffney, hereby declare as follows:

1. I am a citizen of the Irish Republic and a resident of Great Britain presently residing at 27 Milton Road, Harpenden, Hertfordshire, United Kingdom.

2. I am a former Visiting Professor in the Department of Medicine at the University of Leuven, Belgium and in the Department of Human Anatomy and Physiology at University College, Dublin, Ireland. I am currently an Honorary Senior Research lecturer in the Academic Department of Surgery at St. Thomas's Hospital, London, United Kingdom.

3. My academic background and experience in the field of the present invention are listed in the attached curriculum vitae.

4. I have read the reference Trese et al. that I understand is being construed by the United States Patent and Trademark Office as using plasmin to cause vitreal liquefaction.

5. By way of this declaration, I intend to demonstrate that Trese et al., while reporting to the contrary, actually: (a) created a preparation containing a high percentage of streptokinase-plasminogen complex and only a small amount of free plasmin; (b) streptokinase-plasminogen complex has very little proteolytic activity; and (c) that the

inconsistent liquefaction recited in Trese et al. is therefore attributable to the predominant species in their preparation being this streptokinase-plasminogen complex.

6. Trese et al. created a preparation containing primarily the streptokinase-plasminogen complex and only a small amount of plasmin. In the original paper of Trese et al. (1), the authors have described an approximate 1:1 molar ratio mixture of streptokinase (SK) and plasminogen (Plgn) as an adjunct in vitreous surgery. It is known that such a mixture gives rise to a reasonably stable SK-Plgn complex, which has the ability to activate plasminogen to plasmin (2,3). It would seem that this equimolar complex has an active site exposed, which allows interaction with small chromogenic peptides (e.g., S-2251 or Chromozym – PL) such that the assay of this complex is the most common and effective method to assay intact plasminogen in plasma (4). The interaction of SK with Plgn is quite complex and has been reviewed. The review summarizes the composition and behavior of the various complexes derived from the combinations of SK and Plgn (5). Streptokinase does not form an activator complex with all vertebrate plasminogens and has a specificity for human, primate, cat and other species of plasminogen, while not reacting with bovine and some other plasminogens (6,7).

7. The SK-Plgn complex has very little proteolytic activity, while it can degrade casein slowly. The major biological purpose of the SK-Plgn complex is to activate the proenzyme plasminogen to active plasmin.

8. There is a consensus that effective plasminogen to plasmin conversion with SK is achieved by generating a small amount of activator by adding a small quantity (less than 10%) of SK to the plasminogen solution. The resultant small quantity of the SK-Plgn will rapidly activate the remaining plasminogen to plasmin. The procedure for obtaining

plasmin in the current patent application involves mixing approximately 11.3 nmoles of plasminogen derived from 22 mls of autologous plasma with 1.3 nmoles of SK. This should (as described above) yield 1.3 nmoles of the SK-Plasminogen (SK-Plgn) activator complex and this, in turn, will rapidly convert the residual 10 nmoles of plasminogen to active plasmin. This procedure is expected to give a more hydrolytically active preparation with a greater possibility of consistency from preparation to preparation. Conditions of storage prior to use should be such (e.g. 4°C or below) as to reduce the autodegradative process, which would reduce the potency of a preparation. This degradation can be monitored by electrophoretic assessment of the hydrolytic cleavage of the active site chain by plasmin (8).

9. The following references are cited as part of this declaration:

(1) Trese, MT, Williams, GA, Hartzer, MK (2000) Ophthalmology; 107, 1607-1611.

(2) Robbins, KC, Summaria, L, Hsieh, B, Shah, RJ. (1967) J Biol Chem; 242, 2333-2342.

(3) Reddy, KNN, Markus G. (1974) J Biol Chem; 249, 4851-4857.

(4) Gaffney, PJ (1998) In: Laboratory Techniques in Thrombosis – a Manual. (eds: J Jespersen, RM Bertina, F Haverkate) Kluwer Academic Publishers, Netherlands, pp 247-255.

(5) Robbins, KC, Markus, G. (1977) In Fibrinolysis – Current Fundamental and Clinical Concepts (Eds. PJ Gaffney, S. Barkuv-Ulutin) Academic Press, London, pp 61-75.

(6) Wulf, RJ, Mertz, ET. (1969) Can J Biochem; 47, 927-931.

(7) Siefring, GE, Castellino, FJ. (1976) J Biol Chem; 251, 3913-3920.

(8) Gaffney, PJ, Brasher, M, Lord, K, Kirkwood, TBL (1977) Haemostasis; 6, 72- 88.

10. Thus, to summarize, the recitation in Trese et al. as to plasmin enzyme being the active species injected into eyes is simply incorrect. According to the method by which Trese et al. indicates on page 1608 for "Preparation of Autologous Plasmin Enzyme," I am

convinced that the resulting material was not in fact plasmin but instead a streptokinase-plasminogen complex as I have described above. Since it is my understanding that this reference has been cited in the course of the patent process for disclosing plasmin injection at 0.4 units, it is my assertion that following the procedure of Trese et al. the vast majority of the 0.4 units injected was in fact streptokinase-plasminogen complex. Thus, Trese et al. does not in fact show the use of 0.4 units of plasmin as a therapeutic reagent to induce PVD.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Patrick J. Gaffney

Date: Oct 30, 2003

APPENDIX C

RELATED PROCEEDINGS

There are no decisions that have been rendered by a court or the Board in any proceeding identified in the related appeal.